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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/289,576	04/09/1999	RICHARD C. ALLEN	398802000600	8803

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MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	20

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Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No.	Applicant(s)	
	09/289,576	ALLEN ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-17 and 19-40* is/are pending in the application.

4a) Of the above claim(s) *19-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-17 and 37-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed August 27, 2002 (Paper No. 19) has been entered. Claims 1, 8, 9, 11, and 37-39 have been amended.

Accordingly, Claims 1-6, 8-17, and 19-40 remain pending in the instant application.

Claims 19-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in Paper No. 10.

Thus, Claims 1-6, 8-17, and 37-40 are examined herein.

This application contains claims 19-36 drawn to an invention nonelected without traverse in Paper No. 10. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Continued Prosecution Application

The request filed on August 27, 2002 (Paper No. 18) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/289,576 is acceptable and a CPA has been established. An action on the CPA follows.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-6, 8-17, and 37-40 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-6 of the Office Action of Paper No. 12 (mailed 5/7/01) and on pages 2-6 of the Office Action of Paper No. 16 (mailed 2/27/02), as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for providing dopamine or a dopamine precursor to a subject with schizophrenia in an amount effective to alleviate a negative symptom of schizophrenia, a pharmaceutical composition comprising therapeutic cells and Sertoli cells, a pharmaceutical composition comprising therapeutic cells, protective cells, and support cells, and a kit comprising therapeutic cells, protective cells, support cells, and a support matrix.

At page 6, paragraph 3 of the response, Applicants assert that Davis et al. (1991) states that "the negative/deficit symptom complex of schizophrenia may be associated with low dopamine activity in the prefrontal cortex" and "that the hypofrontality found in schizophrenic patients can be redressed by increasing dopamine activity in the prefrontal cortex." However, it is a huge leap to go from a suggestion to increase dopamine activity in the prefrontal cortex as a treatment for schizophrenic patients to actually providing an enabled protocol for achieving the desired treatment effect. As discussed in the previous two Office Actions, the etiology of schizophrenia is not well-understood and treatment of the disease is generally limited to treating specific symptoms (National Institute of Mental Health, Schizophrenia, 1999, pp. 6-7). Although **dopamine blocking agents** have been shown to be effective in treating the symptoms of schizophrenia, the effect of dopamine **replenishment** in specific areas of the brain is not known. Furthermore, the specification does not adequately teach a protocol, as claimed, that could be used to effect the required level of dopamine replenishment. The specification does not disclose what level of dopamine delivery would be therapeutic. It does not teach the level of gene expression required, the

number of transduced cells needed, when or for how long the gene should be expressed, or the frequency of administration of the transfected therapeutic cells (and/or protective cells and support cells). Further, the specification does not teach which combinations of therapeutic cells, protective cells, and support cells would work, nor does it even offer a starting point. The specification discloses a wide variety of cell types that could be used, but does not offer a starting point with regards to a combination of therapeutic cells, protective cells, and support cells that would be effective in treating the negative symptoms of schizophrenia. The skilled artisan is left with the task of testing all these parameters and coming up with a protocol that produces the intended effect. Thus, the skilled artisan would be required to engage in undue experimentation to come up with a protocol that produces the intended effect.

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

The courts have stated that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-504, 190 USPQ 214, 217-219 (CCPA 1976)). However, in the instant case, there is no teaching of either a starting point or the direction in which experimentation should proceed, and trial and error experimentation does not constitute routine experimentation.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and

physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

At page 7, paragraph 4 of the response, Applicants point to their arguments at page 6 of their previous response, submitted November 5, 2001. Applicants assert that they presented evidence that administration of cells as described in the present invention has been successful in the amelioration of a deficit dopaminergic state at particular locations in the brain. However, the study referred to is a study of patients with Parkinson's Disease (PD). The Examiner has already addressed this evidence at page 5, paragraph 2 of the Office Action of Paper No. 16. To reiterate, for reasons of record, the usefulness of dopamine replenishment in the prefrontal cortex of schizophrenics is unpredictable. Further, the level of dopamine expression required and attainable in PD patients is likely to be different than that required and attainable in schizophrenic patients, given that the etiology of these two diseases is different. Further, given that the etiology of schizophrenia is not well-understood, it is unpredictable whether the causative process that leads to mesofrontal dopamine deficits will permit adequate replenishment of dopamine in that area of the brain or if it will continually destroy the newly available dopamine, thereby maintaining a dopamine deficit irrespective of the production of dopamine in the region. Given the poor understanding of the etiology of schizophrenia, the fate of dopamine precursors produced in the prefrontal cortex of a diseased brain is unpredictable. Applicants have not addressed these arguments.

At page 7, paragraph 5 through page 8, paragraph 2 of the response, Applicants argue that the specification provides guidance and direction for the selection of therapeutic cells, protective cells, and support cells that could be used in the claimed methods. Applicants point to pages 12-17, which teaches that "[c]ells useful in the practice of various aspects of this invention include cells of neural origin, paraneural cells such as RPE cells and chromaffin cells, cells engineered by somatic cell hybridization, cells derived from the adrenal medulla and cells that have been genetically engineered to produce biologically active factors." The specification goes on to discuss a variety of cell types that could be used

as support cells and protective cells. Thus, the Examiner maintains that the specification discloses a wide variety of cell type that could be used, but does not offer a starting point with regards to a combination of therapeutic cells, protective cells, and support cells that would be effective in treating the negative symptoms of schizophrenia. The specification does not disclose a single example of a protocol that produces the claimed effect. Thus, the skilled artisan is left with the task of testing all the parameters discussed in the specification to come up with a protocol that produces the intended effect. For the reasons discussed above, this would constitute undue experimentation.

Given the lack of specific guidance in the instant specification for producing the claimed effect of treating the negative symptoms of schizophrenia, the limited working examples, the unpredictable state of the art with respect to *ex vivo* gene therapy and cell-based therapies, the broad scope of the claims, encompassing the use of any cell type as therapeutic, protective, or support cells, one of skill in the art would have been required to engage in undue experimentation to practice the claimed methods and to make compositions as claimed, useful for the treatment of schizophrenia.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,750,103 (Cherksey, 1998) and U.S. Patent No. 5,942,437 (Sanberg et al., 1999)

Claim 37 is directed to a pharmaceutical composition comprising therapeutic cells and Sertoli cells, wherein the therapeutic cells and the Sertoli cells are adhered to a support matrix. Claim 38 is

directed to a pharmaceutical composition comprising therapeutic cells, protective cells and support cells, wherein the therapeutic cells, protective cells, and support cells are adhered to a support matrix. Claims 39 and 40 are directed to a kit comprising therapeutic cells that produce dopamine or a dopamine precursor, protective cells, support cells, and a support matrix, wherein the therapeutic cells, protective cells, and support cells can be adhered to the support matrix.

Cherksey (1998) discloses therapeutic cells that produce dopamine and which are adhered to a support matrix. Cherksey specifically discloses retinal pigment epithelial (RPE) cells and chromaffin cells adhered to the surface of a support matrix (see Claims 1 and 7). Given that RPE cells are also defined as protective cells within the context of the instantly claimed invention (see page 9, lines 20-23) of the instant specification), the embodiments disclosed by Cherksey satisfy the limitation of including protective cells in the composition as disclosed.

At Column 3, lines 51-65, Cherksey teaches co-grafting chromaffin cells "with other cells or substances which promote specific parameters of differentiation. Furthermore, glial cells may have specific regional effects and produce neuronal growth factors." At Column 3, lines 62-65, Cherksey teaches "that co-transplanting cells providing the desired neurotransmitters along with specific types of glia which produce glial-derived factors, may promote neuronal growth and the desired differentiation of grafted cells." See also Column 3, line 66 through Column 13, line 40 and Examples. The glial cells meet the limitation of "support cells" as recited in the instant claims. The instant specification states, at page 9, lines 30-31, that "[s]uitable support cells for use in the instant invention include glial cells." Cherksey does not specifically teach the use of Sertoli cells as recited in Claim 37.

Sanberg et al. (1999) teaches the use of Sertoli cells in transplantation methods (entire disclosure). Sanberg et al. teaches that Sertoli cells are used "as a source for trophic factors to improve viability and growth of cells/tissues for transplantation" and further teaches "improving survival of a graft *in situ* by treating the graft *in situ* with sertoli-cell conditioned media or Sertoli cells" "The cells for

transplantation can include ... other dopaminergic cells for treatment of Parkinson's Disease." Sanberg et al. teach that "co-transplantation with Sertoli cells can provide sufficient local immunosuppression so as to eliminate the need for systemic immunosuppression ... the Sertoli cells will not only provide inhibition of the immune response, but will allow enhanced growth and viability of allografts and xenografts by concomitant trophic support" (Column 10, lines 35-47). Example 5 of Sanberg et al. teaches transplanting "Sertoli cell/chromaffin cell co-grafts" into the brain.

Therefore, it would have been obvious to have modified the compositions of Cherksey, given the co-grafting teaching of Cherksey, by inclusion of Sertoli cells in the composition, as taught by Sanberg et al., because of the expectation of reaping the disclosed benefits.

It would have been obvious to put the cells and the support matrix in suitable packaging (as recited in Claim 39) or in separate containers (as recited in Claim 40) to produce a kit because, as Cherksey discloses multiple cell types and multiple support matrices suitable for use in the method disclosed by Cherksey, the availability of the cells and the support matrices in separate containers would be desirable so that specific combinations of cell type and support matrix could be conveniently obtained.

Therefore, the claimed compositions would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Tiffiany Tabb, whose telephone number is (703) 305-1238.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE BAKER
PATENT EXAMINER